RECEIVED
CENTRAL FAX CENTER
MAY 17 2007

ARGUMENTS/COMMENTS

Claims 1-4 are pending and under consideration in the application.

Specification

The specification has been objected to because it allegedly contains a flow chart. The Examiner has requested deletion of the alleged "flow chart" and substitution thereof with a drawing pursuant to 37 CFR 1.81.

It is respectfully submitted that while it would be relatively simple to make the requested amendment, such amendment would be inappropriate and contrary to normal practice. Chart A at page 5 of the specification is not a "flow chart." It instead falls under the category of a chemical formula, which is expressly permitted and preferred under 37 CFR 1.58(a). A "flow chart" is, within normal patent practice, a schematic, graphic or pictorial summary or presentation that shows the steps, sequence, and relationship of various steps involved in performance of a process. In contrast, the chemical reaction formula shown in Chart A at page 5 of the specification shows a reactant (a chemical compound, not a process step), a product (a chemical compound, not a process step) and a reaction arrow pointing away from the reactant and toward the product. While it is not impermissible to show a chemical reaction in a drawing, it is more typical or conventional to show a chemical reaction within the text of a patent specification.

There are at least about 189 issued patents that include in the specification a chemical reaction of the type printed at page 5 of Applicant's specification (i.e., a chemical formula showing a reactant, a product, and an arrow pointing away from the reactant to the product) which expressly refer to the reaction in the specification as a "chemical reaction formula." There are also at least about 94 patents having a chemical reaction in the specification (formula with reaction arrow) that refer to the reaction in the specification as a "chemical reaction scheme," and at least about another 81 patents that refer to it as a "chemical reaction equation." There are at least about another 50,214 patents in which a chemical reaction equation in the specification is preceded by the words "by the chemical reaction. . .." It is respectfully submitted that there is ample evidence that Applicant's inclusion of a chemical

RECEIVED
CENTRAL FAX CENTER
MAY 17 2007

reaction scheme, formula or equation in the specification is appropriate, conventional and authorized by the patent rules.

On the other hand, there is not a single example of an issued U.S. patent in which a chemical reaction, equation, formula or scheme is referred to as a "flow chart."

It is respectfully submitted that the Examiner is requesting Applicants to make an inappropriate, unconventional and unnecessary amendment.

It is expected, and earnestly requested, that the Examiner withdraw the objection to the specification because of the appropriateness of including chemical formulae in a specification and the relatively unconventional practice of including a chemical formula in a drawing.

Rejection Under 35 U.S.C. §103

Claims 1-4 stand rejected under 35 U.S.C. §103 as being unpatentable over Kim et al. (US 2002/0025951 or WO 01/47945) in view of Berge et al. The Examiner has stated that "Kim et al. teaches the instantly claimed compound," that Berge et al. disclose "the chemical, biological, physical and economic characteristics of medicinal agents can be manipulated and optimized by conversion to a salt form," and that the "claimed salts are *prima facie* obvious based on the teachings of the prior art and the level of skill of the ordinary artisan in the pharmaceutical art."

It is respectfully submitted that the applied references, rather than providing evidence that the claimed invention is within the level of skill of the ordinary artisan in the pharmaceutical art, teaches that the claimed invention is not within the level of skill of the ordinary artisan in the pharmaceutical art. First, it should be noted that Kim et al. does not teach the claimed compounds. To the contrary, Kim teaches the free base form of the compound, not the hydrochloride or hydrobromide forms, as claimed. Rather than teaching the claimed compounds and their salt forms, Kim et al. discloses nothing about the claimed compounds or their salt forms, or any other salt forms for that matter.

The Berge et al. reference does not mention either the claimed compounds or the free base form of the claimed compounds, but instead teaches (page 1, left column, last 3 lines) that choosing an appropriate salt to optimize chemical, biological, physical and economic characteristics of medicinal agents "can be a very difficult task, since each salt imparts unique

properties to the parent compound." Berge et al. further state (page 1, right column, lines 7-13) that:

> Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound. Furthermore, even after many salts, of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation profiles.

The difficult selection process according to Berge involves many detailed considerations relating to physiochemical properties such as dissolution rate, solubility, organoleptic properties, stability and other miscellaneous properties including surface tension, deaggregation behavior and ion-pair extraction effects; bioavailability issues, including formulation effects such as absorption alteration, and pharmacokinetics; general pharmacy considerations such as pharmacological effect; and toxicological considerations.

In conclusion, Berge et al. state (page 16, left column, under "CONCLUSIONS") that "selecting a salt form that exhibits the desired combination of properties is a difficult semiempirical choice," and that "few generalizations are available to predict the effect of particular salt forms on the characteristics of a drug."

Thus, rather than teaching or suggesting the claimed invention, Berge et al. provide evidence showing the difficulty involved in choosing the appropriate salt, and the unpredictability of the effect of choosing a particular salt form. While Berge et al. express optimism that "perhaps in time it will be possible to evolve increasingly more powerful generalizations regarding the effect of a salt on the properties of its parent compound," Berge et al. expressly teach that this time has not yet arrived and that the selection of an appropriate salt form of any particular drug is a difficult, unpredictable endeavor involving more than routine experimentation.

Rather then teaching the claimed salts, Kim et al. disclose the base compound and purification thereof by flash column chromatography. Flash column chromatography does not provide a "well- characterized" product that would meet FDA standards for use as an active pharmaceutical ingredient. If a suitable salt form were obvious, it would have been disclosed by Kim et al. This would allow simple well-characterized purification using standard

recrystallization techniques. Despite the need for a crystalline form of the drug neither Kim et al. nor anyone else were able to find one, until Applicant succeeded seven years after the original disclosure of the base drug.

The fact that Kim et al. were unable to disclose the hydrochloride, hydrobromide or any other salt forms of the base compound despite recognized advantages thereof illustrates that the appropriate salt forms were not obvious. The disclosure of the advantages of salt forms of active pharmaceutical ingredients and the difficulty of discovering appropriate salt forms in the same prior art reference (the Berge) provides further evidence that the claimed invention is not obvious.

Because there is nothing specific in the Berge et al. prior art reference relating to the claimed compounds or the base form of the claimed compounds, the Examiner's rationale in this case could be applied to any pharmacologically active compound. In essence, the Examiner is suggesting that all newly discovered salt forms of any pharmacologically active compound are *prima facie* obvious in view of Berge et al., which teaches the difficulty and unpredictability of selecting an appropriate salt form of a pharmacologically active base compound.

In view of the above remarks, it is respectfully submitted that the application is in condition for allowance and notice of the same is earnestly solicited.

Respectfully submitted,

May 17, 2007
Date

Gunther J. Evanina, Registration No. 35502
Price, Heneveld, Cooper, DeWitt & Litton, LLP
695 Kenmoor, S.E.
Post Office Box 2567
Grand Rapids, Michigan 49501
(616) 949-9610

GJE/dac